Placental transport: a function of permeability and perfusion\textsuperscript{1–4}

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ABSTRACT
Studies in ovine fetus and placenta have pointed to an interaction between the fetal liver and the placenta. The supply of amino acids and carbohydrates depends on this interaction. These studies have led to clinical studies in normal and high-risk pregnancies. The objective of the present review was to compare changes in fetal circulation, in terms of both velocimetry and actual blood flow measurements, and to couple such data with data on the placental transport of amino acids. Flow studies were carried out on the umbilical vein with measurements of time-averaged velocity and venous diameter. A similar approach was used for measurements of ductus venosus flow. Stable-isotope-labeled amino acids were used to study placental transport by the non–steady state approach. The studies of flow showed a marked reduction in umbilical blood flow even when expressed per kilogram fetal body weight in fetal-growth-restricted pregnancies. This may be coupled with an increased ductus venosus shunt, the combination leading to a marked reduction in fetal hepatic blood flow. The placental transport of some amino acids is reduced in fetal-growth-restricted pregnancies. Furthermore, non–glucose carbohydrates and polyols are found in fetal blood, some in concentrations higher than maternal concentrations. There is significant uptake of several polyols and of mannose across the umbilical circulation in normal pregnancies. In conclusion, both perfusion and permeability can now be studied in both normal and high-risk pregnancies.

KEY WORDS Blood flow, velocimetry, amino acids, placental transport, fetal metabolism, placental metabolism

INTRODUCTION

Recently, attention has been focused on permeability characteristics of the placenta. This is due, in large part, to the advent of techniques permitting the identification of membrane-bound specific transporters in the placenta for amino acids, glucose, and fatty acids. Knowledge of the types of transporters on the maternal and fetal surfaces of the trophoblast is a necessary first step in understanding permeability. One must also determine the concentration of each of the transporters on the 2 surfaces (ie, transporter no./cm\textsuperscript{2}) and the total surface of the placenta in different disease states. Most of this information is still not available however.

On the perfusion side, progress has been made in human pregnancies moving from velocimetry measurements alone to measurements of blood flow. From a nutritive viewpoint, the latter is critical. Several studies have reported human umbilical blood flow throughout gestation in uncomplicated pregnancies (1–4) with reasonably good agreement among studies. Measurements of uterine blood flow, however, have been much more difficult to obtain.

The placenta has the unique characteristic of being perfused by 2 independent circulations: the umbilical circulation and the uterine circulation. Furthermore, most of the blood flow in the umbilical vein goes directly into perfusion of the fetal liver (5). Only by viewing these 2 organs as an integrated organ system can we understand some of the metabolic characteristics of the conceptus. For example, glutamine has a large transplacental flux into the fetal circulation from the maternal circulation. But this does not represent its carbon contribution to the fetus. As the umbilical blood flow perfuses the fetal liver, the glutamine is converted to glutamate through the action of glutaminase, and the glutamate leaves the liver in large amounts. It is then extracted by the placenta from the fetal circulation. Many other such metabolic cycles exist between the 2 organs, including the lactate-pyruvate and serine-glycine cycles.

In animals, it is feasible with tracer methodology to dissect the various unidirectional fluxes across the placenta. The data we have acquired for the essential amino acid leucine are summarized in Figure 1 (6–8). Note that the 3 fluxes entering and leaving the umbilical circulation are of approximately equal magnitude. Thus, the net umbilical uptake, representing the dietary supply to the fetus, is equal to any one of those 3 fluxes in magnitude.

If we use the principal of conservation of mass to compare the quantity of each amino acid leaving the uterine circulation and entering the placenta with the quantity entering the umbilical circulation, we can estimate the utilization rate of amino acids by the uteroplacental tissues. This is summarized in Figure 2 for a normal ovine pregnancy (9). There is a large placental utilization of the branched-chain amino acids, some of which are transaminated to alpha ketoacids and contribute to placental ammonia

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\textsuperscript{2} Presented at the conference “Maternal Nutrition and Optimal Infant Feeding Practices,” held in Houston, TX, February 23–24, 2006.

\textsuperscript{3} Supported by National Institutes of Health grant 5 RO1 HD034837-07, Fetal Velocimetry & Amino Acid Transport in Pregnancy, and grant number M01 RR00069, General Clinical Research Centers Program, National Centers for Research Resources, National Institutes of Health.

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production. The utilization of serine is primarily directed at glycine production through the action of serine hydroxymethyltransferase. The large umbilical uptake of glycine is a consequence of serine utilization. Glutamate is also taken up from the fetal circulation and utilized predominantly for oxidation within the placenta, although a small amount is utilized for glutamine production.

**INTERACTIONS OF THE FETAL LIVER AND PLACENTA**

To fully understand placental function and its effect on fetal nutrition, we must consider the placenta and fetal liver as an integrated organ system. This was brought out in the earlier discussion of glutamine-glutamate exchange, but it applies to much more than those amino acids (10).

Data from late gestation ovine pregnancies are presented in Figure 3. Note that the interconversion of serine-glycine in the placenta also occurs in the fetal liver, with a large hepatic uptake of glycine and release of serine. In general, the uptake of amino acids by the fetal liver is very large. As illustrated in Figure 4, under normal conditions, the huge fetal hepatic uptake of gluconeogenic amino acids and lactate and glucose is compensated, in part, by the significant hepatic release of glutamate and pyruvate, which can then be taken up and oxidized within the placenta, thus reducing the oxygen requirements of the fetal liver (11). When fetal hepatic glucose release is stimulated by fetal glucagon

**FIGURE 1.** Unidirectional fluxes of leucine into and out of the placenta measured in vivo under steady state conditions. The data are abstracted from the following references: Loy et al (7) and Ross et al (6). Note that the 3 major fluxes that together determine umbilical uptake are of approximately equal magnitude. KIC, α-ketoisocaproate. Reprinted with permission from reference 8 (Figure 3, page 154).

**FIGURE 2.** Mean (±SE) uteroplacental amino acid utilizations that were significantly different from zero, expressed per 100 g placenta and ranked by magnitude (negative utilization = production). *P < 0.05, **P < 0.01, ***P < 0.001. P values were determined by Student’s t test for paired samples. Reprinted with permission from reference 9 (Figure 4, page E18).

**FIGURE 3.** Comparison of arteriovenous differences (µmol/L) of individual amino acids and ammonia (NH₃) across the fetal left hepatic lobe and umbilical circulation. Reprinted with permission from reference 10 (Figure 2, page E912).

**FIGURE 4.** Fetal hepatic uptake and output of glucose carbon and gluconeogenic substrate carbon under normal physiologic conditions (control) and during a glucagon-somatostatin infusion into the fetal circulation. Each number represents a substrate carbon-to-oxygen uptake molar ratio. Reprinted with permission from reference 11 (Figure 4, page E547).
infusion, glutamate output is markedly reduced. This illustrates the fact that hepatic glutamate release compensates in part for the absence of hepatic glucose release during fetal development.

### TABLE 1
Stable-isotope clearance for the 9 essential amino acids across the ovine placenta

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>Clearance $\text{mL min}^{-1} \cdot \text{kg}^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methionine</td>
<td>$17.1 \pm 3.0$</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>$15.6 \pm 1.8$</td>
</tr>
<tr>
<td>Leucine</td>
<td>$14.1 \pm 1.3$</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>$14.4 \pm 2.1$</td>
</tr>
<tr>
<td>Valine</td>
<td>$12.5 \pm 2.0$</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>$7.0 \pm 2.4$</td>
</tr>
<tr>
<td>Threonine</td>
<td>$4.1 \pm 0.8$</td>
</tr>
<tr>
<td>Histidine</td>
<td>$3.7 \pm 0.7$</td>
</tr>
<tr>
<td>Lysine</td>
<td>$2.9 \pm 0.6$</td>
</tr>
</tbody>
</table>

$^1$ All values are $\bar{x} \pm$ SD. Data are from reference 12.

### ESSENTIAL AMINO ACID FLUX

Shown in Figure 5 are data from a study in uncomplicated ovine pregnancies (12). The 9 essential amino acids were given

### FIGURE 5
Amino acid enrichments for the first (A) and second (B) infusates in maternal artery (△), uterine vein (▲), umbilical vein (●), and fetal artery (○). Time 0 is the start of the isotope bolus injection. Infusate A contained the 5 amino acids shown in the left column, and infusate B contained the 5 amino acids shown in the right column. Reprinted with permission from reference 12 (Figure 1, page E34).

### FIGURE 6
Pulse flux calculated over the first 10 min after the bolus versus maternal plasma arterial concentration (MAT ART CONC) for the 5 essential amino acids that had high and similar pulse flux clearances. Reprinted with permission from reference 12 (Figure 4, page E37).
as a bolus infusion into the maternal circulation, and their uni-
directional fluxes into the fetal circulation were measured. The in
vivo data illustrate the fact that some essential amino acids have
a much higher maternal plasma clearance across the placenta
than do others, as shown in Table 1. Lysine, for example, has a
placental clearance of only 20% that of leucine. When the
pulse fluxes of the 5 essential amino acids crossing rapidly are
compared, it is clear that the magnitude of the flux is a function
of the amino acid’s normal maternal concentration, as shown
in Figure 6.

CLINICAL SEVERITY IN FETAL GROWTH
RESTRICTION

Many clinical studies have been conducted of fetal growth
restriction (FGR) pregnancies. It has become clear that metabolic
and circulatory findings in the fetus and placenta are a function
of the severity of FGR. This is not simply a matter of the degree
of fetal reduction in body size for a given gestational age. To
begin to address clinical severity for studies of FGR pregnancies,
we use a simple classification based on 2 of the obstetric mea-
urements most commonly made in these pregnancies. These are
the measurements of umbilical artery pulsatility index (PI) and
the pattern of the fetal heart rate (FHR) (13).

This classification for all infants defined as having FGR on the
basis of a reduction in abdominal circumference of \( \geq 2 \) SDs from
normal for that gestational age is presented in Table 2. Thus,
although all these fetuses are small, we found that if both the FHR
and the PI were normal (group 1), none of the infants had hypoxia
or acidosis. By contrast, groups 2 and 3 did, with an incidence of
\( \approx 70\% \) in group 3 (13). Other studies established that the trans-
placental glucose gradient also increased in groups 2 and 3 (14),
as shown in Figure 7. Also, in studies of the transplacental flux
of \([^{13}\text{C}]\text{leucine, the fetal/maternal enrichment ratio reflected the}
clinical severity as well, which is shown in Figure 8 (15). Each
year, more information both circulatory and metabolic is being
collected in FGR pregnancies. Hence, the assessment of clinical
severity is constantly being improved for individual pregnancies.
However, grouping FGR pregnancies into 3 classes on the basis
of PI and FHR has been useful for the interpretation of some of
the metabolic data. As more information about fetal circulation is
collected, clinical severity and fetal well-being can be much
more precisely determined. For example, presented in Figure 9
are data obtained in a sequential study of FGR pregnancies that
were followed biweekly with fetal velocimetry (16). That study
found that some velocimetry indexes changed relatively early
(i.e., \( \geq 2 \) wk before delivery), whereas others were more ominous

### Table 2

<table>
<thead>
<tr>
<th>Umbilical artery velocimetry</th>
<th>Fetal heart rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>Normal</td>
</tr>
<tr>
<td>Group 2 (Elevated PI)</td>
<td>Normal</td>
</tr>
<tr>
<td>Group 3 (Elevated PI)</td>
<td>Abnormal</td>
</tr>
</tbody>
</table>

\( \text{PI, pulsatility index. Data are from reference 13.} \)

### Figure 7

Measured mean (±SD) values of maternal arterial-umbilical venous glucose concentration differences in appropriate-for-gestational-age (AGA) fetuses and in fetal-growth-restricted (FGR) cases of groups 1, 2, and 3. The \( P \) values refer to the significance of the differences for the intercepts of the AGA versus the FGR groups (solid lines) and among the FGR groups (dashed lines) for the regression analysis of the maternal-fetal difference versus gestational age. No significant differences were found among the slopes of these regressions. Data are from reference 14 (Figure 2, page 940).

### Figure 8

Leucine enrichment ratios in appropriate-for-gestational-age (AGA) and fetal-growth-restricted (FGR) human pregnancies (left) and in control and FGR ovine pregnancies. The data for the human pregnancies are from Marconi et al (15); those for the ovine pregnancies are from Regnault et al (unpublished observations, 2006). MPE, mass percent excess.

### Figure 9

Cumulative onset time curves of Doppler abnormalities for each fetal vessel examined. Time 0 refers to the date of delivery. MCA PI, middle cerebral artery pulsatility index; UA AEDF, umbilical artery absent end diastolic flow; DV S/a, ductus venosus wavefrom; UA RF, umbilical artery reversed flow; PA PV, pulmonary artery peak velocity; DV RF, ductus venosus reversed flow; AO PV, aortic artery peak velocity. Reprinted with permission from reference 16 (Figure 1, page 142).
and changed within the last week before delivery. Such information can help us to better interpret transport data and also help in selecting pregnancies for which one or another form of therapy could be applied.

Despite the circulatory and placental pathology in FGR pregnancies, amino acid uptake into the fetal circulation can be increased for some amino acids by increasing maternal concentrations. As shown in Figure 10 (17), when maternal concentrations of branched-chain amino acids were increased, the umbilical vein-artery difference was found to be increased as well.

**PLACENTAL AND FETAL HEPATIC CIRCULATIONS**

With the advent of techniques to measure umbilical vein and fetal hepatic vein blood flow in human pregnancies, studies have shown that FGR fetuses can have reduced flows. As shown in Figure 11, even when flow is corrected per kg fetal body wt, there is a very large reduction in umbilical flow, especially in FGR groups 2 and 3 (18). The percentage reduction is ≈60%.

The fact that the ductus venosus plays a significant role in determining the shunting of blood away from the fetal liver is illustrated in Figure 12. That this, in fact, does occur in some FGR pregnancies is shown in Figure 13 (20). The combined effect of a reduced umbilical blood flow and an increased ductal shunt away from the liver can be dramatic, as shown in Table 3. One can certainly anticipate hepatocellular damage in such cases.

![FIGURE 10. Relation of umbilical amino acid differences to oxygen content differences (UMB AA/O2) and maternal concentrations (MAT CONC) (in μmol/L) for branched-chain amino acids in experimental (solid symbols) and control (open symbols) groups. Reprinted with permission from reference 17 (Figure 3, page 481).](image)

![FIGURE 11. Umbilical vein blood flow per kilogram fetal weight versus gestational age in growth-restricted fetuses: group 1, □; group 2, ◇; group 3, ▲. Continuous lines represent the 5th, 10th, 90th, and 95th percentiles from 70 normally grown fetuses. Reprinted with permission from reference 18 (Figure 1B, page 435).](image)

![FIGURE 12. Anatomical scheme of the umbilical venous return indicating the 4 sites of measurement. 1, intra-amniotic umbilical vein; 2, intrahepatic umbilical vein; 3, ductus venosus inlet; 4, ductus venosus outlet. Reprinted with permission from reference 19 (Figure 1, page H1257).](image)

![FIGURE 13. The percentage ductus venosus shunt is shown for a group of intrauterine-growth-restricted (IUGR) fetuses and for a group of normal pregnancies. It is clear that shunt is significantly higher in the IUGR fetuses than in the normal fetuses. Data are from reference 20.](image)

**TABLE 3**

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>FGR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mL/min</td>
<td>mL/min</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>62.3 ± 51.7</td>
<td>23 ± 31.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Right</td>
<td>51.5 ± 44.6</td>
<td>1.8 ± 37.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Total</td>
<td>113</td>
<td>25</td>
<td>—</td>
</tr>
</tbody>
</table>

FGR, fetal growth restriction. Data are from reference 20. 

1 SD (all such values).
SUGAR AND POLYL CONCENTRATIONS DURING FETAL DEVELOPMENT

Many studies have been made of maternal-fetal glucose concentrations, of glucose umbilical uptake, and of the regulation of glucose by insulin. From a nutritional viewpoint, however, few studies have been carried out of the other nonglucose carbohydrates and polyols represented in this group in present terms of their fetal and maternal concentrations in Table 4 (21, 22). The data are for 2 species, including data collected in ovine and in human pregnancies. Note that many of the polyols are at higher concentrations in fetal blood. Some of the sugars and polyols represented in Table 4 are also at higher concentrations in fetal blood. Of even more interest are the data presented for the 2 species in Figure 14. Despite very low maternal plasma concentrations, umbilical uptake of mannose in both species is significant.

This fetal mannose uptake is a function of maternal concentrations, of glucose umbilical uptake, and of the regulation of glucose by insulin. From a nutritional viewpoint, however, few studies have been carried out of the other nonglucose carbohydrates and polyols represented in this group in present terms of their fetal and maternal concentrations in Table 4 (21, 22). The data are for 2 species, including data collected in ovine and in human pregnancies. Note that many of the polyols are at higher concentrations in fetal blood. Of even more interest are the data presented for the 2 species in Figure 14. Despite very low maternal plasma concentrations, umbilical uptake of mannose in both species is significant.

This fetal mannose uptake is a function of maternal concentration, as shown in Figure 15. These data strongly suggest the presence of a high-affinity mannose transporter in the placenta for both species. The data also lead us to hypothesize that a requirement exists for an external supply of mannose from the mother rather than meeting fetal requirements entirely from mannose production from glucose.

No financial support was received by the author other than the grant support listed.

REFERENCES


TABLE 4
Carbohydrate concentrations in humans and sheep

<table>
<thead>
<tr>
<th></th>
<th>Humans</th>
<th>Sheep</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maternal</td>
<td>Fetal</td>
</tr>
<tr>
<td></td>
<td>artery</td>
<td>artery</td>
</tr>
<tr>
<td>Inositol</td>
<td>28.7 ± 1.8</td>
<td>91.1 ± 6.0</td>
</tr>
<tr>
<td>Fructose</td>
<td>56.6 ± 11.4</td>
<td>42.2 ± 4.2</td>
</tr>
<tr>
<td>Glucose</td>
<td>4686 ± 131</td>
<td>2981 ± 94</td>
</tr>
<tr>
<td>Mannose</td>
<td>75.1 ± 3.1</td>
<td>60.3 ± 3.0</td>
</tr>
<tr>
<td>Sorbitol</td>
<td>1.71 ± 0.74</td>
<td>1.5 ± 0.2</td>
</tr>
<tr>
<td>Ribitol</td>
<td>5.6 ± 2.7</td>
<td>11.7 ± 1.6</td>
</tr>
<tr>
<td>Arbutin</td>
<td>0.8 ± 0.6</td>
<td>1.1 ± 0.8</td>
</tr>
<tr>
<td>Erythritol</td>
<td>4.2 ± 2.5</td>
<td>11.4 ± 4.4</td>
</tr>
<tr>
<td>Maltose</td>
<td>11.4 ± 4.4</td>
<td>2.6 ± 1.5</td>
</tr>
<tr>
<td>Fructose</td>
<td>56.6 ± 11.4</td>
<td>42.2 ± 4.2</td>
</tr>
</tbody>
</table>

All values are mean ± SD. Data are from references 21 and 22.

FIGURE 15. Maternal (M) and fetal (F) mannose concentrations are compared for a group of normal pregnancies. The relation is highly significant, with fetal concentrations being significantly lower than maternal, which implies placental transport. $F = 14.68 \times 0.597 M; R^2 = 0.478, P < 0.001$. Data are from reference 22.